THEORETICAL STUDIES ON THE CHEMISTRY OF QUATERNARY AMMONIUM COMPOUNDS

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INTRODUCTION

In an earlier project in this laboratory involving the preparation of 1, 4- and 1, 5-tertiary diamines (1), evidence was found of amine exchange reactions between quaternary ammonium salts and secondary amines according to the general equation

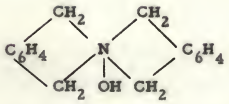
$$(R'R_3N^+)X^- + R''R'''NH \longrightarrow R_3N + R'R''R'''N + HX$$

This stimulated an interest in this type of reaction. The work described here has been an attempt to shed some light on the mechanism of the reaction through the use of optically active compounds. This approach has been previously used in studying carbon-carbon alkylations employing quaternary ammonium salts (2), but apparently has not been used in studying the reactions of these salts with amines.

Derivatives of α-phenylethylamine have been chosen for this project because in addition to possessing an asymmetric carbon atom, they should exhibit the reactivity of the benzyl group, which is one of those known to migrate in this type reaction (3). The specific reaction chosen is that between N, N, N-trimethyl-α-phenylethylammonium bromide and di-n-butylamine.

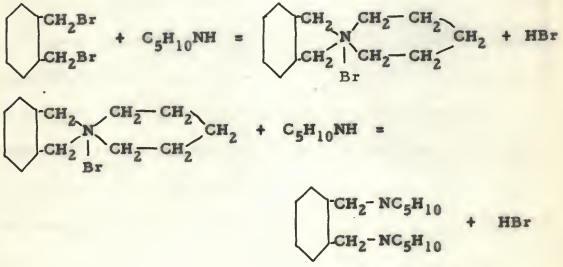
REVIEW OF THE LITERATURE

A brief paragraph discussing amine exchange reactions is included in a comprehensive review of carbon-carbon alkylations with amines and ammonium salts appearing in volume seven of "Organic Reactions" (4). The earliest reference in this section is to the work of Max Scholtz. In 1891 Scholtz (5) published work concerning the action of ammonia on o-xylene bromide. He had hoped to obtain xylene diamine and then through the splitting out of ammonia to obtain the imine. When he heated the o-xylene bromide with a ten-fold quantity of ammonia in a sealed tube, he obtained a crystalline compound which showed an analysis of $C_{16}H_{16}NBr$. He concluded that this compound had resulted from the reaction of two molecules of o-xylene bromide and one molecule of ammonia with the escape of three molecules of HBr. From chemical tests Scholtz concluded that this compound was not the hydrobromide of an amine. When he reacted this material with silver oxide, he obtained a substance to which he attributed the structure:



In light of present knowledge it can be seen that if this were the case, the original compound must have been a quaternary ammonium bromide.

In later publications (6), Scholtz used this proposed compound in explaining results of the action of primary, secondary, and tertiary amines on o-xylene bromide. His experimental results led him to believe that reactions of certain of these amines took place in a step-wise fashion as shown in the example of the reaction between o-xylene bromide and piperidine (6):



According to this reaction, a secondary amine has displaced the quaternary nitrogen on one of the carbons. Julius von Braun (3, 7, 8), in a series of publications dealing with the relative stability of cyclic bases, also investigated the action of organic amines upon quaternary ammonium halides (3). In mentioning the work of Scholtz, von Braun pointed out that the former proposed formulas, which in view of later knowledge should form rather stable rings. According to von Braun the tendency of groups to migrate was of the following decreasing order: allyl, benzyl, and methyl (3). He prepared a number of quaternary ammonium compounds and reacted them with amines, obtaining evidence of amine exchange. For example, he was able to obtain dibenzylamine from the reaction between trimethylbenzylammonium bromide and benzylamine. As an additional product of the reaction, he obtained trimethylamine.

Later it was found that quaternary ammonium salts also undergo reaction with the cyanide ion and compounds with active methylene groups such as acetoacetic ester and malonic ester (9). In addition, Snyder, Smith, and Stewart (9) also found that a heterocyclic nitrogen compound, gramine methiodide, was more reactive than salts containing the benzyl group in reactions of this type.

In the case of certain Mannich bases, it was found that the tertiary amines would undergo amine exchange reactions (10). It

was proposed that the mechanism of this reaction proceeded through the elimination of an amino group and subsequent addition of another amino group to the unsaturated compound thus formed. Snyder and Eliel (11) then experimented with 1-methylgramine which could not undergo amine elimination. It was found that in the presence of an acid catalyst amine exchange took place, apparently proceeding by a substitution reaction. When the catalyst was not present, no reaction took place. Snyder and Brewster (12) found that both β-dimethylaminopivalophenone and its methiodide failed to alkylate or undergo amine exchange reactions. This was not unexpected. Amine elimination is impossible for the amine of the structure:

$$C_6H_5 - \overset{O}{\overset{\|}{C}} - \overset{CH_3}{\overset{|}{C}} - CH_2N(CH_3)_2$$
$$\qquad\qquad\quad CH_3$$

and its methiodide, while steric hindrance of the α-methyl groups prevents an S_N2 reaction, and S_N1 amine replacements are hindered because no resonance stabilized carbonium ion can be formed.

Thermal decompositions of quaternary ammonium compounds have also been investigated. Decomposition of benzyltrimethylammonium hydroxide by thermal means was found to yield both benzyl alcohol and methanol according to the following equation (13):

$$\left[C_6H_5CH_2\overset{+}{N}(CH_3)_3\right]OH^- \longrightarrow C_6H_5CH_2OH + (CH_3)_3N \quad (65\%)$$
$$\searrow C_6H_5CH_2N(CH_3)_2 + CH_3OH \quad (35\%)$$

In further investigation of this type of reaction by the use of benzhydryltrimethyl ammonium hydroxide $(C_6H_5)_2CHN(CH_3)_3OH$, Ingold and Hughes (13) found that the proportion of methanol formed was higher than that of benzhydrol. From the fact that the proportionate yield of methanol was increased upon the addition of OH^- ion, they concluded that the reaction by which the methanol was formed was dependent upon the concentration of both anion (OH^-) and cation (quaternary ammonium ion) and was, therefore, bimolecular. They believed the reaction by which the benzhydrol was formed to be dependent only upon the concentration of the cation and therefore of unimolecular nature. In a subsequent publication they proposed that these decomposition reactions might follow one of two courses. In course A, which takes place according to equation (A), a carbonium ion is formed and the reaction is first order. (14).

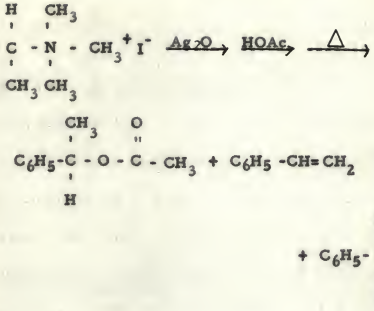
$$R\text{--}\overset{+}{N}R'R''R''' \longrightarrow R^+ + NR'R''R'''$$
$$R^+ + X^- \longrightarrow RX \quad (A)$$

Course B, which takes place according to equation (B), is a second order reaction.

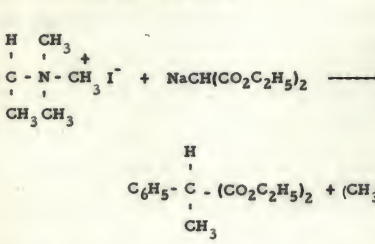
$$\left[R'R''R'''\overset{+}{N}-\overset{\curvearrowright}{R}\right]X^- \longrightarrow R'R''R'''-N + RX \qquad (B)$$

They felt that if the cationic stability of R were progressively increased, or if the basicity of X^- were progressively decreased, a stage at which reaction A should predominate over reaction B should be reached. In this manner they explained the variety of products obtained in these reactions.

In the opinion of Snyder and Brewster (2) carbon-carbon alkylations appeared to be analogous to the formation of benzyl alcohol and benzyl chloride by thermal decomposition of quaternary benzylammonium hydroxides and chlorides. Knowing that the mechanism of substitution could determine configurations, they employed stereochemical methods in their investigations. When they degraded d-(+)-N, N, N-trimethyl-α-phenylethylammonium acetate, they obtained a 26.3% yield of l-(-)-α-phenylethyl acetate, showing 98-100% inversion of configuration. Complete inversion is characteristic of S_N2 reactions (15). As the following equation shows, in addition to the l-(-)-α-phenylethyl acetate, a 33.1% yield of styrene and a 12.2% yield of N, N-dimethyl-α-phenylethylamine were obtained.



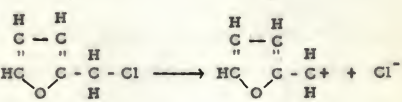
The N, N-dimethyl-α-phenylethylamine which was recovered had retained a high percentage of its optical activity. In the reaction of d-(+)-N, N, N-trimethyl-α-phenylethylammonium iodide with sodiomalonic ester according to the equation:



the α-methylbenzylmalonic ester formed was inactive. Complete racemization is characteristic of S_N1 type reactions (16). In this

case, however, they did not conclude that the reaction could not be of the S_N2 type, because the recovery from the reaction of some N, N-dimethyl- α-phenylethylamine which was only weakly dextro-rotatory indicated that racemization of the quaternary ammonium iodide may have taken place before it could participate in the alkylation.

Eliel and Peckham (17) continued studies of the alkylations and amine exchange reactions using substituted furfurylamines. They found the reactivities of the methiodidies of furfuryldimethylamine and of 5-methylfurfuryldimethylamine in the alkylations of sodium cyanide and piperidine to be no greater than that of benzyldimethylamine. From the alkylation of sodium cyanide with the methiodide of furfuryldimethylamine they drew some conclusions regarding the mechanism of the reaction. Furfuryl chloride was known to react with sodium cyanide to yield principally a rearrangement product (18), 2-methyl-5-cyano-furan. This result can be explained by the formation of a carbonium ion, which is stabilized by resonance structures as shown in the following equations:



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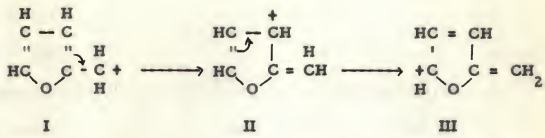
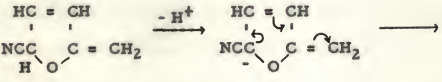
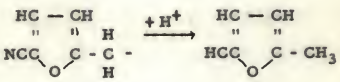


I II III

The cyanide ion reacts with the cation indicated as structure III. If the resulting intermediate loses a proton, shifts in the manner shown below, and the resulting carbanion regains the proton, 2-methyl-5-cyano-furan will be formed.





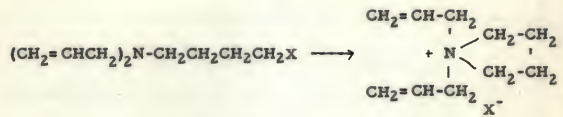
According to this explanation of the behavior of furfuryl chloride, structure III portrays the most stable carbonium ion. Because of this, Eliel and Peckham reasoned that if a carbonium ion were formed as an intermediate in the alkylation using furfuryltrimethylammonium iodide, this reaction should also yield large quantities of the rearrangement product. When the latter reaction produced principally the normal nitrile and only minor quantities of the rearranged

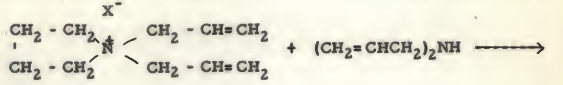
product, they concluded that the experimental data could be interpreted most satisfactorily on the basis of an S_N2 type reaction, in which the cyanide ion would attack the alkyl carbon before the amino group departed.

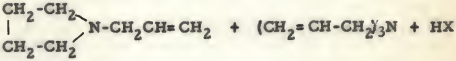
Butler and Angelo (1) encountered another example of amine exchange when they attempted to prepare 1, 4-bis-(diallylamino)-butane and 1, 5-bis-(diallylamino)-pentane by the reaction of the 1, 4- and 1, 5- dihalo and di-(arlysulfonoxy)-alkanes with diallyamine. The desired products were not obtained. The products of the reaction of the 1, 4-derivatives with an excess of diallylamine were allyl-pyrrolidine and triallylamine and the products of the reaction of the 1, 5-derivatives with an excess of diallylamine were allylpiperidine and triallylamine. They found that the results could be explained on the basis of an intramolecular cyclization to the five- or six-membered cyclic quaternary ammonium salt, followed by an amine exchange reaction of the quarternary ammonium salt with the excess diallyl-amine to produce triallylamine and the appropriate allyl substituted heterocyclic amine. This reaction scheme is outlined in the following equations which use the 1, 4-derivative as an example:

$$X\text{-}CH_2CH_2CH_2CH_2X + 2\,(CH_2{=}CH\text{-}CH_2)_2NH \longrightarrow$$

$$(CH_2{=}CH\text{-}CH_2)_2NCH_2CH_2CH_2CH_2X + (CH_2{=}CHCH_2)_2NH\cdot HBr$$







By suitable experiments they showed that the reactions shown could take place. This theory is supported by the fact that it has been shown (19) that amines of the type $X(CH_2)_{\underline{n}}NR_2$ yield $(CH_2)_{\underline{n}}\overset{+}{N}R_2X^-$ when $\underline{n}$ has a value of 4, 5, or 6. The authors (1) found that acceptable yields of 1,4- and 1,5-bis-(dialkylamino)-alkanes had been prepared (20) by the reaction of the di-(arylsulfonates) of the corresponding glycols with dialkylamines. When they employed this method with diallylamines, they obtained unsatisfactory results. The fact that the yield of (dibenzylamine)-pentane reported (20) in this reaction was only 10% gave added support to the theory of an amine exchange type reaction since the allyl and benzyl groups are known to migrate in these reactions. In the case of the successful preparation of the 1,4- and 1,5-bis-(dialkylamino)-alkanes the tendency of the rings to rupture was probably greater than that of the alkyl groups to migrate. Butler and Angelo (1)

felt that the tendency of the allyl and benzyl groups to migrate was due to their ability to stabilize a carbonium ion through the number of resonance forms which they were capable of attaining, and that the reaction had a mechanism involving the carbonium ion.

EXPERIMENTAL

GENERAL CONSIDERATIONS

A. Source of chemicals: With the exception of those compounds whose preparations are described in the text, the sources of the chemicals used in this project were as follows:

dl- α-Phenylethylamine	Brothers Chemical Co.
dl-N, N-Dimethyl- α-phenylethylamine	Brothers Chemical Co.
Methyl bromide	The Matheson Co., Inc.
HBr (anhydrous)	The Matheson Co., Inc.
Styrene	Carbide and Carbon Chemicals Co.
di-n-Butylamine	Carbide and Carbon Chemicals Co.
Trioxymethylene (paraformaldehyde)	Fisher Scientific Corp.
Formic acid (90%)	Victor Chemical Co.
n-Butyl bromide	Columbia Organic Chemicals, Inc.
NaOH (CP)	Fisher Scientific Corp.
d-Tartaric acid	Eastman Chemical Co.

B. Analyses: The carbon, hydrogen, and nitrogen analyses were made by Dr. G. Weiler - Dr. F. B. Strauss Microanalytical

Laboratory, 164 Banbury Road, Oxford, England. The bromide analyses were made according to the Volhard method described in a book by Pierce and Haenisch (21).

C. Physical measurements: All temperatures are recorded in degrees Centigrade and are uncorrected. Pressures below 10 mm. were checked against a McLeod gauge and those above 10 mm. were read from a Zimmerli gauge. Refractive indices were measured by means of an Abbe refractometer.

The measurements of optical rotations were made on a Rudolph Model 80 High-Precision polarimeter having as its smallest scale division 0.002 degree. Samples were allowed to come to equilibrium with the temperature of the air-conditioned room in which the instrument was housed, and the temperatures recorded are those of the room at the time the readings were made. A sodium vapor lamp served as a light source.

For pure liquids specific rotations were calculated according to the formula (22):

$$[\alpha]_D^t = \frac{a}{ld}$$

where $[\alpha]_D^t$ is the specific rotation at temperature t referred to the D line of sodium (5,893Å), a is the angular rotation, l is the length of the column of liquid in decimeters, and d is the density of the liquid.

For the solutions the specific rotations were calculated according to the formula:

$$[\alpha]_D^t = \frac{a\ 100}{l\ c}$$

where a is the angular rotation l is the length of the column of liquid in decimeters and c is the concentration of solute expressed in grams per 100 ml. of solution.

The molecular rotation $[M]_D^t$ is computed according to the equation:

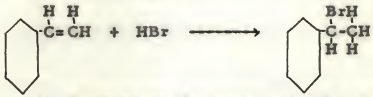
$$[M]_D^t = \text{molecular rotation} = \frac{[\alpha] \times MW}{100}$$

This value is useful in comparing different salts of the same base. All salts of an optically active base should have very nearly the same rotation per gram equivalent (23).

Wherever possible, rotations were measured on pure liquids. Because of the small amounts of some of the compounds it was necessary to measure them in solution. In these cases solutions of the compounds to be compared were of similar concentrations and contained the same solvent. This was necessary because specific rotation varies with the concentration and with the solvent (24).

PREPARATION OF COMPOUNDS

A. Preparation of α-phenethyl bromide

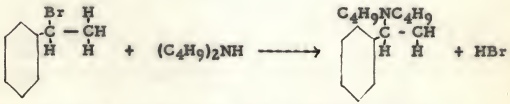


Into a weighed three-necked flask equipped with a thermometer, gas addition tube, and a reflux condenser with an outlet tube attached to a funnel inverted over a solution of NaOH was placed 154.6 grams (1.49 moles) of freshly distilled styrene. Dry hydrogen bromide from a cylinder was passed into the reaction vessel, which was cooled by means of an ice-salt bath. Periodically the progress of the reaction was checked by means of weighing the reaction flask. After an addition period of seven and one-half hours, during which the reaction mixture was held at a temperature of approximately 5° C., fumes were observed escaping through the funnel. The flow of HBr was cut off and the mixture was allowed to sit in the bath for an additional half hour. At the end of this time the flask and contents were weighed and the gain in weight was found to be 132.5 grams. The theoretical gain should have been 120 grams. The mixture was allowed to warm gradually by allowing the ice bath to melt. Water was added to the mixture and a dilute solution of K_2CO_3 was added until the aqueous layer was neutral to litmus. The heavier lower layer was

separated and washed several times with water. It was then left to dry over anhydrous K_2CO_3. The dried liquid was placed in a 500 ml. round-bottom flask equipped with a thermometer-well and the material was distilled under reduced pressure through a short unheated column packed with Berl saddles. A yield of 218.6 grams (79.6% of the theoretical) of a liquid boiling between 92.5° and 96° at pressures of 15.8 mm. to 17.2 mm. was obtained. The recorded boiling points for this compound are: 91-91.5° at 16 mm. (25) and 97° at 17 mm. (26) and 85° at 13 mm. (27). The value $n_D^{22.5°} = 1.5605$, was found. The recorded value at 20° C. is 1.5612 (27). This compound seemed somewhat unstable and tended to become discolored rather rapidly.

B. Preparation of N,N-di-n-butyl-∝-phenylethylamine

The desired compound was prepared twice according to this general equation:



The preparations differed only in the fact that in one the hydrogen bromide produced was neutralized by sodium carbonate, and in the other it was absorbed by an excess of di-n-butylamine.

Procedure a: In the first preparation 64.5 grams (0.5 mole) of di-n-butylamine (b.p. 157.5-159.5° C.) and 26.5 grams (0.25 mole) of sodium carbonate were placed in a 500 ml. round-bottom flask equipped with a mechanical stirrer, a reflux condenser, and an addition funnel. Into the funnel was placed 93.9 grams (0.5 mole) of ∝-phenylethyl bromide. The amine was heated to reflux temperature by means of an electric heating mantle. The heat was removed and addition of the bromide was begun. After approximately half of the bromide had been added, heat was applied again. Total addition time was twenty minutes. By this time a foamy white slush had formed and the heat had to be withdrawn. The reaction mixture was cooled by an ice bath. After an hour of stirring the foam had subsided and the mantle was

again placed under the flask. At the end of three days, during which the mixture had been heated and stirred, 350 ml. of water was added to the mixture through the condenser while stirring was continued. The solid dissolved and two layers formed. The upper, organic, layer was separated and washed three times with 100 ml. portions of water. It was then dried over C. P. sodium hydroxide pellets.

Since no data concerning this compound could be found in the literature, it was necessary to experiment with distillation conditions. The liquid was placed in a round-bottom flask equipped with a thermometer-well and attached to a short unheated column packed with Berl saddles. At atmospheric pressure, when the pot temperature reached 210°, nothing had begun to distill. The pot was allowed to cool and the pressure was lowered to 17.3 mm. of mercury. At this pressure a 5.6-gram fraction with a boiling range of 50-54.5° C. was collected. The next fraction weighed 5.3 grams and boiled from 55° C. to 58° C. at a pressure of 16.9 mm. of mercury. The third fraction, which weighed 8.6 grams, consisted of material boiling from 70° C. to 96° C. at a pressure of 16.7 mm. of mercury, material boiling from 90° C. to 140° C. at a pressure of 10 mm. of mercury, and material boiling up to a temperature of 115° C. at a pressure of 3 mm. of mercury. In order to achieve distillation of this high boiling fraction it was necessary to heat the column by means of an electric heating

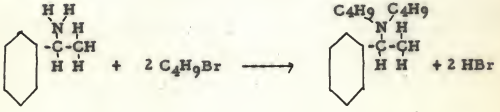
tape. A yield of 63.1 grams of a clear liquid boiling at 115° -117° C. at a pressure of 3 mm. of mercury was obtained. Since this boiling range was much higher than that of either of the reactants, it was presumed to be the desired compound. The weight obtained represents 54.3% of the theoretical yield. A refractive index determination gave the value, $n_D^{24} = 1.4921$. The compound was found to have a density of 0.8865 g/ml. at 25° C. The material was redistilled and found to have a boiling point of 113° C. to 114° C. at a pressure of 2.8 mm. of mercury. At 21° C. it had a refractive index of 1.4931.

For future identification purposes a picrate was prepared from this compound. About 25 drops of the amine was mixed with 10 ml. of a saturated solution of picric acid in methanol. After the solution had been refluxed for one hour, it was chilled in an ice-salt bath until crystals separated. The crystals were removed by suction filtration. After recrystallization from 95% ethanol the crystals were dried in a vacuum desiccator. The compound had a melting point range of 92-96° C.

Procedure b: In the second preparation 129 grams (1.0 mole) of di-n-butylamine was placed in a 500 ml. three-necked flask equipped with mechanical stirrer, reflux condenser, and dropping funnel. The amine was heated by means of an electric heating mantle to reflux temperature and dropwise addition of 92.5 grams (0.5 mole)

of ∝-phenylethyl bromide was begun. Total addition time was about forty minutes. A solid was formed and the mixture became slushy. Heating and stirring were continued for a total reflux time of about 17 hours. After the mixture cooled, the hydrobromide which had formed was hydrolyzed by the addition of 650 ml. of a 1 normal solution of sodium hydroxide. The lower layer was removed and the top layer was washed with three successive portions of distilled water. Completeness of washing was determined by testing the wash water with silver nitrate. The top layer was poured into an Erlenmeyer flask and dried over C. P. sodium hydroxide pellets. The dried liquid was distilled through a column packed with Berl saddles and heated by means of an electric heating tape. Seventy-one grams (61% yield) of a colorless liquid boiling at 114-116° C. at 3 mm. was obtained. Analysis of the compound gave: C, 82.45%; H, 11.68%; N, 5.94%. The calculated values are: C, 82.33%; H, 11.66%; N, 6.00%.

Procedure c: As additional evidence in proving the structure of this compound, it was prepared by a third method according to the empirical equation:



In this case, a mixture of 60 grams (0.5 mole) of α-phenylethylamine and 127 grams (1.0 mole) of n-butyl bromide was heated on a steam bath for approximately three hours. When the reaction mixture was allowed to cool, it became quite viscous. To this material 100 grams of a 20% solution of sodium hydroxide (0.5 mole) was added with thorough shaking. The upper layer which separated was placed in a one liter three-necked flask. The lower layer weighed 135 grams, indicating that HBr had been removed in the aqueous layer. Since the organic layer did not seem to react when it was heated on a steam bath, it was heated by means of an electric heating mantle to 140° C. for three hours. Upon cooling the mixture was very viscous and contained some crystals. After 200 grams of 20% sodium hydroxide solution was added, the mixture was stirred with heating on a steam bath. The upper layer was separated and dried over solid sodium hydroxide. The material was distilled at a pressure of 1 mm. of mercury with a boiling range of 107° - 110° C. The refractive index at 22° C. was 1.4910. The infra-red spectrum of this compound proved to be idential with that of the compound prepared according to procedure b. A yield of 68.5 grams (58.5%) of the theoretical was obtained.

The products obtained from the three different preparations are compared in Table 1.

TABLE I

COMPARISON OF N, N-DI-n-BUTYL- α-PHENYLETHYLAMINE PREPARED BY SEVERAL PROCEDURES

Procedure	% Yield	n_D/t	B. P. °C. /mm. Hg	Analysis Obs.	Calcd.
a	54.3	1.4931/21°*	113-114/2.8*		C=82.33 H=11.66 N= 6.00
b	61.0	1.4908/22°	114-116/3	C=82.45 H=11.68 N= 5.94	C=82.33 H=11.66 N= 6.00
c	58.8	1.4910/22°	107-110/1		C=82.33 H=11.66 N= 6.00

* Redistilled sample

C. Resolution of N, N-di-n-butyl-∝-phenylethylamine

In the initial attempts to resolve this amine the method described by Ingersoll in "Organic Reactions" (28) for the resolution of dl-∝-phenylethylamine was used as a guide. Since this method involved the use of l-malic and d-tartaric acids, small quantities of the N, N-di-n-butyl-∝-phenylethylamine were dissolved in aqueous solutions of these acids in an attempt to effect resolution. The use of d-tartaric proved successful. In this case 10 grams of the amine was added to a solution of 6.5 grams of d-tartaric acid in 26 ml. of water. The mixture was heated on the steam bath for more than an hour and then allowed to cool slowly. No crystals had separated by the following day, but when the solution was observed after five days, it contained a large white crystal which had formed on the end of the stirring rod and when the solution was agitated slightly, many fine white crystals separated. The crystals were filtered on a Buchner funnel and air dried. They were found to have a melting point of 85° - 95° C. The melting point of d-tartaric acid is 170° C. In addition, the specific rotation for this salt in water was higher than that of d-tartaric acid.

Without further recrystallization the crystals obtained in this preparation were used for seed crystals in a subsequent preparation using larger quantities of starting materials.

To a solution of 22.5 grams of d-tartaric acid in 90 ml. of

water was added 35 grams (0.15 mole) of the tertiary amine. The mixture was heated on a steam bath until solution of the amine was complete. It was then removed from the steam bath, allowed to cool, and seeded with a crystal from the previous resolution attempt. The crop of crystals which formed was removed by filtration on a Buchner funnel and washed with cold water. The filtrate was evaporated to less than the original volume of the solution on the steam bath. After the solution had cooled, it was seeded with a crystal from the first crop. A second crop of crystals formed after a few hours and was separated in the same manner as the first crop. The filtrate was treated in the same fashion as that from the first crystallization, and this process was repeated until the filtrate became quite viscous and no more crystals would form. The fractions were then recrystallized as follows: About two-thirds of the first crop was dissolved in three times its weight of water by heating on a steam bath, allowed to cool and seeded with a crystal from the remaining one-third of this fraction. The crystals which formed were removed by suction filtration and washed with water. The remainder of this crop was dissolved in the filtrate, the volume of the solution was reduced by evaporation on a steam bath and crystallization brought about as before. This procedure of dissolving each fraction in the filtrate from the preceding crop was continued until all fractions had been recrystallized. A second recrystallization

was performed in the same manner.

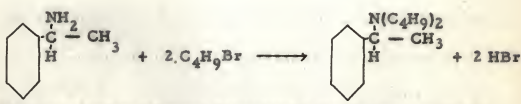
A total of 13.3 grams of the salt (0.038 mole) was hydrolyzed using 50 ml. of 2 normal sodium hydroxide solution. The free amine was extracted with benzene and dried over C. P. sodium hydroxide pellets. After the benzene had been removed by distillation at atmospheric pressure, the pressure was reduced and the amine was obtained. A 5-gram fraction boiling at 114° - 116° C. at a pressure of 3 mm. of mercury was obtained. This represented a yield of 28.5% of the theoretical.

In methanol solution the following values for the specific rotation were obtained:

$$[\alpha]_D^{21.5} = +14.91^\circ \quad (c = 3.4680)$$
$$[\alpha]_D^{21.5} = +15.35^\circ \quad (c = 2.6252)$$

The fact that this compound could be resolved proves that the structure contains an asymmetric carbon atom, which in turn proves that substitution is on the alpha carbon.

D. Preparation of optically active N, N-di-n-butyl-α-phenylethylamine



This preparation followed Procedure c for the preparation of N, N-di-n-butyl-α-phenylethylamine. An active form of the primary amine was used. The levo form of α-phenylethylamine was obtained by resolution of the racemic mixture according to the procedure of Ingersoll (28). The optical purity of this amine ($[\alpha]_D^{23.5} = -32.47°$) was estimated to be 86.3 per cent.

In a 200 ml. round-bottom flask equipped with a reflux condenser 14.7 grams (0.12 mole) of l(-)-α-phenylethylamine and 36.2 grams (0.26 mole) of n-butyl bromide were mixed and heated on a steam bath for 2 hours. The mixture developed a reddish brown color and upon cooling became solid. After the reaction mixture had cooled, twenty-five grams of 20% sodium hydroxide solution was added to the solid in the flask and the mixture was heated on the steam bath until the solid was broken up and two liquid layers were formed. The aqueous lower layer was drawn off and the upper layer was placed in a three-necked flask equipped with a mechanical stirrer and a reflux condenser. This material was heated by means of an electric heating mantle for a total of three hours. The temperature rose to 142° during

the third hour. Fifty grams of a 20% solution of sodium hydroxide was added to the viscous liquid formed upon cooling. The mixture was stirred with heating (not over 100° C.) until two well-defined liquid layers were formed. The upper layer was dried over C. P. sodium hydroxide pellets overnight. The dried liquid was distilled at reduced pressure. A yield of 11.1 grams (39.2% of the theoretical) of a material boiling at 113° - 115° C. (2.8 mm.) was obtained. The infrared spectrum of this material was identical with that of the previously prepared N,N-di-n-butyl-α-phenylethylamine.

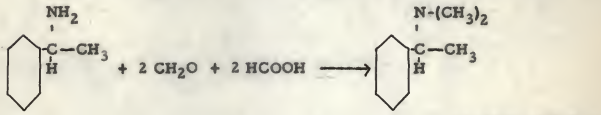
When the pure liquid was placed in a 1 decimeter polarimeter tube, average rotations of +10.310° or -169.688° were obtained, depending upon the direction in which the scale was rotated. It will be noted that these readings are 180° apart. Since the sample obtained from the amine exchange reaction would be too small to measure as the pure liquid and would have to be run in a solvent, a determination of the rotation of this amine in methanol was made to serve as a basis of comparison. In this solvent the following values were found:

$$[\alpha]_D^{22.5} = -9.43° \quad (c = 3.8348)$$

$$[\alpha]_D^{22.5} = -8.65° \quad (c = 2.1092)$$

These values represent a maximum optical purity of 63% based on the value obtained for d-(+)-N,N-di-n-butyl-α-phenylethylamine when it was prepared through resolution of the racemic mixture.

E. Preparation of optically active N, N-dimethyl- α-phenylethylamine



Numerous attempts were made to resolve the commercially available N, N-dimethyl- α-phenylethylamine. When it was dissolved in an aqueous solution of l-malic acid according to the procedure which proved successful with α-phenylethylamine (28), no crystals separated. Evaporation of the solution in stages only produced a very viscous solution. Substitution of acetone, methanol, and ethanol as solvents produced no better results. The same results were obtained when d-tartaric acid was used. After a period of approximately six weeks had elapsed some crystals separated from a very viscous solution containing the amine and d-camphorsulfonic acid. The solvent had been ethyl acetate, but most of it had evaporated. Attempts to separate and re-crystallize these crystals failed.

After these procedures failed, a decision was made to attempt to prepare an active form of N, N-dimethyl- α-phenylethylamine by the methylation of the corresponding optical isomer of α-phenylethylamine. An adaptation of the Leuckart Reaction (29) was chosen for this attempt. Details of the preparation were worked out using dl- α-phenylethylamine

before the reaction was used on the active form of the primary amine.

Preparation a: Thirty grams (1.0 mole) of paraformaldehyde and 76.67 grams (1.5 moles) of 90% formic acid were placed in a three-necked, round-bottom flask, equipped with a mechanical stirrer, dropping funnel, reflux condenser, and thermometer. Into the dropping funnel, was placed 60.5 grams (0.5 mole) of α-phenylethylamine. By means of an electric mantle, the mixture in the flask was heated to 50° C., and addition of the amine was begun. The source of heat was removed and an ice bath was employed to keep the temperature in the 50° -60° range while the remainder of the amine was added. The mixture was then refluxed for 15 minutes. After the mixture was cooled to 10° C., 50% sodium hydroxide solution was added slowly to neutralize the excess formic acid. More than twice the quantity of base necessary to neutralize the theoretical excess of 0.5 mole of formic acid was required, and instead of a liquid organic layer, a semi-solid layer was obtained. The results were believed to be due to the fact that the CO_2 formed in the reaction had not been completely driven off. This preparation was abandoned and a new one was begun with fresh materials.

Preparation b: Thirty grams (1.0 mole) of paraformaldehyde and 76.67 grams (1.5 moles) of 90% formic acid were mixed in a three-necked flask equipped in the same manner as described in preparation a.

The mixture was heated to 50° C., and addition of 60.5 grams (0.5 mole) of α-phenylethylamine was initiated. The heating mantle was withdrawn and the temperature was held between 50° C. and 60° C. by means of a cooling bath until all of the amine had been added. Heat was applied again. As the temperature rose, a thick, yellow foam appeared on the surface. When it was heated very slowly, the gas gradually escaped and the layer of foam subsided. As more heat was applied, the temperature rose to 95° - 100° C. The liquid was refluxed at this temperature for a period of two and one-half hours to assure complete expulsion of carbon dioxide. The mixture was then cooled to 10° C. and 50% sodium hydroxide was added slowly. Slightly more than the theoretical quantity (0.5 mole) of sodium hydroxide was required for neutralization of the excess formic acid. The upper, organic, layer was separated and dried over C. P. sodium hydroxide pellets. It was then distilled through a column packed with Berl saddles at a pressure of 10 mm. of mercury. A fraction with a boiling range of 71-73° C. was collected. The yield weighed 53.3 grams and represented 71.5% of the theoretical value. The measurement of the refractive index on this compound showed $n_D^{22} = 1.5040$. The value, $n_D^{20} = 1.5025$, is recorded in the literature (2). Gaseous methyl bromide was bubbled through a solution of the amine in acetone. The resulting solid had a melting point of 190-192° C. and did not depress the melting point

of a known sample of N, N, N-trimethyl- α-phenylethylammonium bromide.

Preparation c: The same procedure was repeated using smaller quantities of the reactants in order to see whether or not a reasonable yield could be obtained when the quantities involved were small. In this case, 25 grams (0.207 mole) of α-phenylethylamine, 12.4 grams (0.414 mole) of paraformaldehyde, and 31.8 grams (0.621 mole) of 90% formic acid were used in the reaction. A yield of 19 grams (61.7% of the theoretical amount) was obtained.

Preparation d: A mixture of 15 grams (0.496 mole) of paraformaldehyde and 38 grams (0.744 mole) of 90% formic acid solution was placed in a three-necked round-bottom flask equipped with mechanical stirrer, dropping funnel, thermometer, and reflux condenser. Thirty grams (0.248 mole) of d(+)- α-phenylethylamine, which had been obtained through resolution of the dl- amine by l-malic acid (28), was placed in the dropping funnel. By means of an electric heating mantle, the mixture in the flask was heated to 50° C. and addition of the amine was begun. The heat was removed and a cooling bath was used to keep the temperature in the 50-60° range while the remainder of the amine was added. The mixture was then refluxed until the evolution of CO_2 appeared to be complete. After the reaction mixture had been cooled

to 10° C., a 50% solution of sodium hydroxide was added slowly to neutralize the excess formic acid. The upper organic layer was separated from the aqueous layer, and benzene extractions of the lower layer were added to the previously separated organic layer. The benzene solution was dried over C. P. sodium hydroxide pellets over night. After the benzene was distilled off, the remaining liquid was distilled through a fractionating column at reduced pressure. A fraction boiling at 71-73° C. at 10 mm. and weighing 20 grams was collected. This represented 54% of the theoretical yield. The following physical constants were recorded:

$$n_D^{22} = 1.5040 \qquad [\alpha]_D^{23.5} = \begin{matrix} +64.22° \\ +64.41° \end{matrix} \quad (l = 2 \text{ dcm.})$$

$$[\alpha]_D^{25} = \begin{matrix} +64.16° \\ +63.94° \end{matrix} \quad (l = 1 \text{ dcm.})$$

The constants recorded in the literature are (2):

$$n_D^{20} = 1.5025 \qquad [\alpha]_D^{26} = +61.76° \quad (l = 1 \text{ dcm.})$$

The specific rotation recorded in the literature was determined from the rotation of a sample of d-(+)-N, N-dimethyl-α-phenylethylamine which had been prepared according to the procedure described in "Organic Syntheses" for the preparation of N, N-dimethyl-β-phenylethylamine (30). This procedure, which also was a Leuckart Reaction (29), differed from the one presented in this paper in a number of details. The molar ratio of amine to formaldehyde to formic acid was 1:3:5

instead of 1:2:3. The formaldehyde was used in the form of a 37% aqueous solution. The mixture was refluxed for eight hours after evolution of CO_2 had ceased. A 4N solution of HCl was added, and the solution was evaporated to dryness before the free base was liberated by 18 N NaOH. Although yields of 74-83% were reported for this method, it appeared to be much more time consuming than the one reported in this paper.

A comparison of the yields obtained in the different preparations is recorded in Table II.

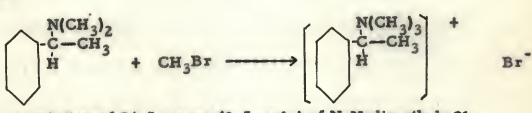
TABLE II

YIELDS OF N, N-DIMETHYL-α-PHENYLETHYLAMINE

Preparation	Quantity of Primary Amine Used		Yield
	Grams	Moles	
a	60.5	0.5	
b	60.5	0.5	71.5%
c	25	0.21	61.7%
d*	30	0.25	54 %

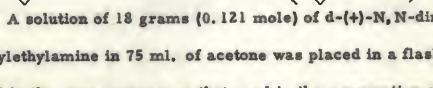
*Preparation of optically active amine

F. Preparation of N, N, N-trimethyl-α-phenylethylammonium Bromide



A solution of 74.5 grams (0.5 mole) of N, N-dimethyl-α-phenylethylamine in 200 milliliters of acetone was placed in a 500 milliliter three-necked flask equipped with a mechanical stirrer, a gas addition tube and a reflux condenser. From the outlet of the condenser a tube led to a trap immersed in a Dry-Ice and acetone mixture. While the mixture was stirred, 50.5 grams of methyl bromide which had been previously condensed in a trap was permitted to bubble slowly into the solution. During this addition the temperature rose spontaneously to a temperature at which the acetone refluxed. After about twenty minutes a white precipitate began to form. Addition of the methyl bromide took about three hours. After this time, one-hundred additional milliliters of acetone was added. The precipitate was filtered on a Buchner funnel, washed with cold acetone, and dried in a vacuum desiccator. A yield of 88.7 grams (73.5% of the theoretical) of a white solid melting at 190-192° C. was obtained. A sample was recrystallized by dissolving it in ethanol and reprecipitating it by the addition of cold ethyl ether. This sample was analyzed by the Volhard method (21). The bromide content found was 32.81%. That calculated for the desired compound is 32.73%.

G. Preparation of d-(+)-N, N, N-trimethyl- α-phenylethylammonium bromide



A solution of 18 grams (0.121 mole) of d-(+)-N, N-dimethyl- α-phenylethylamine in 75 ml. of acetone was placed in a flask equipped in the same manner as that used in the preparation of the optically inactive form of the amonium salt. Gaseous methyl bromide was bubbled through the solution until a considerable excess had collected in the trap. During this process, a beautiful white precipitate formed and the temperature of the reaction mixture rose spontaneously. After the reaction had cooled the solid was separated by suction filtration and was washed with cold acetone. The white crystals were dried in a vacuum desiccator. A yield of 23 grams (78% of the theoretical) was obtained. This material had a melting point of 190-192° C. Analysis revealed a bromide content of 32.29%. The calculated value for this constituent is 32.73%. In aqueous solution the following specific rotations were obtained for this salt: $[\alpha]_D^{24} = +17.36°$ (c = 1.1524)

$[\alpha]_D^{24} = +13.38°$ (c = 0.8556)

Molecular rotations which were calculated for purposes of comparison with that of the quaternary ammonium iodide were:

$$[M]_D^{24} = +42.36^\circ \quad (c = 1.524)$$

$$[M]_D^{24} = +32.67^\circ \quad (c = 0.8556)$$

The specific rotation of the iodide recorded in the literature (2) and the molecular rotation calculated from this value are:

$$[\alpha]_D^{26} = +11.88^\circ \quad (c = 1.2627)$$

$$[M]_D^{26} = +34.57^\circ$$

A comparison of yields, physical constants and analyses of the dl- and d-(+)- forms of N, N, N-trimethyl-α-phenylethylammonium bromide is found in Table III.

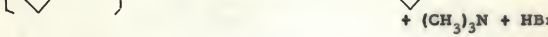
TABLE III

COMPARISON OF dl- AND d-(+)- FORMS OF N, N, N-TRIMETHYL-α-PHENYLETHYLAMMONIUM BROMIDE

Form	Yield	M. P. (° C.)	Br^-	
			Found	Calcd.
dl-	73.5%	190-192	32.81	32.73
d-(+)-	78 %	190-192	32.29	32.73

THE REACTION OF DI-n-BUTYLAMINE WITH N, N, N-TRIMETHYL-α-PHENYLETHYLAMMONIUM BROMIDE

Undoubtedly, these compounds react with one another in more than one way, but the reaction with which this project was concerned is represented by the equation



Of course, in the actual reaction the HBr formed is absorbed by the excess di-n-butylamine.

Before using the optically active quaternary, this reaction was carried out three times using the racemic form. In the first attempt, 23.3 grams (0.096 mole) of the ammonium salt was placed in a round-bottom, three-necked flask, equipped with a mechanical stirrer and a reflux condenser with its outlet attached to a cold trap immersed in a Dry-Ice and acetone mixture. To this solid compound 258 grams (2 moles) of di-n-butylamine (B. P. 158-159° C.) was added and the mixture was heated with stirring. After two hours most of the solid seemed dissolved. After a heating time of about seven hours a white solid again separated. The reaction mixture was allowed to cool after eight and one-half hours of heating.

At the end of the reaction period the gain in weight of the trap was 1.5 grams. A picrate made from the liquid in the trap had a melting point of 205-219° C. The recorded melting point for the picrate of trimethylamine is 216° (225°) (31).

The white solid in the reaction vessel was removed by vacuum filtration. It was composed of sparkling white platelets which seemed quite hygroscopic. After attempts to recrystallize the compound were unsuccessful, it was dried as much as possible in a vacuum desiccator and a melting point determination was attempted. This solid showed a melting point of 183-230° with decomposition. Since the melting point of the original compound was 190-192°, this definitely seemed to be a new compound. It was presumed to be di-n-butylamine hydrobromide.

When the solid was dissolved in a solution of 24 grams of sodium hydroxide in 200 ml. of water, an organic layer separated. The aqueous solution was extracted with three portions of ethyl ether. The ether solution was washed with water and dried over solid potassium hydroxide. It was then combined with the original filtrate which had also been dried over potassium hydroxide. Upon distillation of the resulting solution through a column packed with Berl saddles a 2.5-gram fraction boiling at 113-119° (2.8 mm.) was obtained. This was a very small fraction, the last liquid in the pot, and showed very

obvious signs of decomposition. It was slightly yellow in color. The refractive index value 1.4900 at 22° was lower than found for known N,N-di-n-butyl-α-phenylethylamine, but a picrate made from this fraction showed a melting point of 92-96° and did not depress the melting point of the picrate of the known tertiary amine.

Removal of excess di-n-butylamine in the first attempt was so time consuming that in the second run the molar ratio of amine to ammonium salt was cut to ten to one. This was also more in accord with the amine exchange reaction carried out by Eliel and Peckham (17). Thus, 23.3 grams (0.096 mole) of the quaternary salt was mixed with 129 grams (1 mole) of di-n-butylamine in a reaction vessel equipped as in the previous experiment, and the mixture was heated with stirring for 48 hours.

At the end of this time the gain in weight of the trap was 3 grams. A picrate made from the material in the trap had a melting point of 211-223° C.

The white solid which had precipitated was filtered as before, and was washed with cold ethyl ether. The washings were added to the filtrate and the solid was dried in a vacuum desiccator. The dried material melted with decomposition over the range, 225-267° and weighed 18.6 grams. A Volhard bromide analysis (21) revealed 38.58% bromide content. This compared favorably with the calculated

38.04% bromide of di-n-butylamine hydrobromide. On the basis of 32.81% bromide in the original salt, this also accounted for 93.8% of the bromide originally present.

The filtrate which had been dried over potassium hydroxide was then fractionally distilled. A 7 gram fraction boiling at 115-120° at 3 mm. was obtained. It was also slightly discolored and at 22.5° gave a refractive index of 1.4877, which is low. This represents a crude yield of 31.2%.

The reaction was tried a third time using the same quantities as in the second attempt and following the same procedure. After the mixture had refluxed at a temperature of approximately 150° C. for 48 hours, the cold trap contained two grams of trimethylamine. The solid hydrobromide of di-n-butylamine which separated weighed 18.7 grams. Upon distillation a yield of four grams of a fraction boiling from 114-117° C. at a pressure of 3 mm. of mercury was obtained.

After these preliminary experiments the reaction using the optically active ammonium salt was carried out as follows:

In the equipment already described, 20.5 grams (0.084 mole) of d-(+)-N, N, N-trimethyl-α-phenylethylammonium bromide and 108.4 grams (0.84 mole) of di-n-butylamine were mixed. The mixture was heated with stirring at a slow reflux rate for forty-eight hours. During this period the temperature ranged between 150° C and 160° C. At the end

of the reaction period the trap showed a gain in weight of 1.8 grams. A picrate of this material had a melting point of 215-217° C. which corresponds to the recorded melting point of the picrate of trimethylamine. At the beginning of the reaction the quaternary was not soluble in the di-n-butylamine. After a few hours only a small amount of solid remained in the flask. As heating was continued a new white solid began to precipitate. At the end of the heating period, this solid was collected on a Buchner funnel, washed with ether, and the ether washings were added to the filtrate. The solid had a melting point which was higher than that of the original solid reactant. Analysis showed a bromide content of 38.54%. The calculated bromide content of di-n-butylamine hydrobromide is 38.04%. The filtrate was dried over C. P. sodium hydroxide pellets. Upon distillation at reduced pressure a fraction boiling at 112-113° at 2.8 mm. and having an infrared spectrum identical with that of known N,N-di-n-butyl-α-phenylethylamine was obtained. The weight of this fraction was 3.5 grams, representing a yield of 17.8% of the theoretical. Optical measurements were made on solutions of this fraction in methanol. The following values were obtained:

$$[\alpha]_D^{22.5} = +2.97° \quad (c = 2.1656)$$

$$[\alpha]_D^{22.5} = +3.88° \quad (c = 4.2248)$$

Table IV tabulates the absorption bands in the infrared spectra of different samples of N, N-di-n-butyl-α-phenylethylamine.

TABLE IV

INFRARED SPECTRA ABSORPTION BANDS OF SAMPLES OF N, N-DI-n-BUTYL-α-PHENYLETHYLAMINE

Sample	Absorption Bands μ							
Cpd. prepared as in procedure b*	3.4	6.23	6.85	----	8.55	9.25	----	12.90
Cpd. from procedure c[x]	3.4	6.20	6.85	----	8.55	9.25	----	12.90
l-(-)-	3.4	6.20	6.85	----	8.55	9.25	----	12.90
Product of amine exchange reaction	3.4	6.20	6.85	7.95 (m)	8.55	9.25	12.5 (sh)	12.90

*See page 21.
[x]See page 22.
[m]Medium
[sh]Shoulder

The yields of products obtained from the reaction between N, N, N-trimethyl-α-phenylethylammonium bromide and di-n-butylamine are compared in Table V.

TABLE V

COMPARISON OF YIELDS OF PRODUCTS OBTAINED FROM REACTION BETWEEN N, N, N-TRIMETHYL-α-PHENYLETHYLAMMONIUM BROMIDE AND DI-n-BUTYLAMINE

Trial	Yield of $N(C_4H_9)_2$ C_6H_5 CH CH_3	Recovery of Br^- as $(C_4H_9)_2NH \cdot HBr$	Yield of $(CH_3)_3N$
1	11.1%	-----	26.4%
2	31.2%	93.8%	53.0%
3	17.8%	94.0%	35.2%
4	17.8%	89.9%	36.2%

DISCUSSION

As stated in the introduction the purpose of this investigation was an attempt to shed some light on the mechanism of amine exchange reactions through the use of optically active compounds. Since the work which prompted this interest dealt with the migration of allyl groups (1), it might have seemed logical to use substituted allylamines having asymmetric carbon atoms in this project; however, in view of the fact that allyl groups are known to be capable of undergoing rearrangements (32, 33) which could produce additional complications in the problem, the substituted benzyl group was chosen.

The reaction studied in this project would be considered a nucleophilic substitution since the nitrogen of the dibutylamine has an unshared pair of electrons and would be attracted by the electronically deficient substituted ammonium ion. It has been shown that the mechanism of the nucleophilic substitution can determine the configuration of the product. According to presently accepted theories (34), in a bimolecular nucleophilic substitution, commonly called an S_N2 reaction, a transition complex is formed in which the substituting group and the displaced group are simultaneously attached to the same carbon atom.

The transition state having the incoming and outgoing groups on opposite sides of the carbon should have the lowest internal energy. This leads to inversion of configuration. In cases such as the hydrolysis of an alkyl halide by the OH^- ion, electrostatic effects would also tend to direct the entering anionic group toward the positive end of the carbon-halogen dipole, the side of the carbon atom farther from the halogen atom. This, of course, would produce inversion. Ingold (35) does not consider this to be the true explanation of the inverted configuration. As evidence, he cites two examples in which direction of the dipole in the outgoing group is reversed, and an inverted configuration is still obtained. One of these examples involves the attack of OH^- on the $-\overset{|}{\underset{|}{C}}-NR_3^+$ group. The other example which Ingold offered as proof that oppositely charged groups do not lead to retention of configuration in an S_N2 reaction involves the α-phenylethyldimethylsulfonium ion. Ingold and his co-workers (36) proved that when α-phenylethylchloride and α-phenylethylamine are alike in configuration, they are alike in sign of rotation. In a kinetically controlled experiment, they treated α-phenylethylchloride with the hydrosulfide ion in an S_N2 reaction, and then methylated the product without disturbing the bonds of the asymmetric atom:

$$C_6H_5\text{-}\overset{CH_3}{\underset{(+)}{CH}}\text{-}Cl \xrightarrow[S_N2]{SH^-} C_6H_5\text{-}\overset{CH_3}{\underset{(-)}{CH}}\text{-}SH \xrightarrow{CH_3I} C_6H_5\text{-}\overset{CH_3^+}{\underset{(-)}{CH}}\text{-}S(CH_3)_2$$

The sulfonium compound was then treated with sodium azide, and the alkyl azide was reduced to the amine:

$$C_6H_5\text{-}\overset{CH_3^+}{\underset{(-)}{CH}}\text{-}S(CH_3)_2 \xrightarrow[S_N2]{N_3^-} C_6H_5\text{-}\overset{CH_3}{CH}\text{-}N_3 \xrightarrow[Pt]{H_2} C_6H_5\text{-}\overset{CH_3}{\underset{(+)}{CH}}\text{-}NH_2$$

Thus, in the substitution of the negatively charged azide ion for the positively charged sulfonium group, inversion occurred.

In the apparently unimolecular substitution reactions, commonly referred to as S_N1, the final product may show racemization, inversion, or retention of configuration. This type of substitution apparently passes through a carbonium ion intermediate. The group which is displaced is removed by the solution leaving an electronically deficient carbon atom with a positive formal charge. In most cases this carbon while bonded to only three groups is able to attain a planar configuration instead of the usual tetrahedral structure and the entering groups have equal opportunity to attack either side of the carbon, thus producing complete racemization. If some factor interferes with the ability of this carbon atom to attain a planar configuration, retention of configuration can result. If the carbonium ion contains some group with a

negative charge which can form a weak electrostatic bond with the side of the carbon opposite the receding group until the entering group has become attached, retention will result (37, 38, 39). Some inversion occurs along with the racemization if the departing group remains close enough to the carbonium ion to shield one side somewhat from the entering group and thus favor substitution on the reverse side (40).

Summarizing these conditions, Ingold states the following rules for the spatial orientation of nucleophilic substitution:

"S_N2 Rule: Substitution by mechanism S_N2 involves inversion of configuration, independently of all constitutional details." (15)

"S_N1 Rule: Mechanism S_N1, proceeding through a carbonium ion, involves racemisation, together in general with an excess of inversion, unless a configuration-holding group, such as the α-carboxylate-ion group, is present, when configuration is predominantly preserved." (16)

Ingold states further that the S_N2 rule can be used to prove configuration if the kinetics of the reaction is known. Since a kinetic study was not made on the problem presented here, it was necessary, in order to interpret any results other than complete racemization, to attempt to establish and prove the relationship between the direction of rotation and the configuration of N,N-di-n-butyl-α-phenylethylamine. This was the purpose of the preparation of this

compound from 1-(-)-α-phenylethylamine by the use of n-butyl bromide. It was necessary to assume that the carbon-nitrogen bond in this reaction would not be disturbed and the original configuration would be retained. The product was found to have a levo rotation in methanol solution; however, while the primary amine had a calculated optical purity of 86.3%, the tertiary amine had an optical purity of 63% on the basis of comparison with a methanol solution of the isomer which had been obtained through resolution by means of d-tartaric acid. Assuming that, as in the case of a number of other α-phenylethyl compounds (41), the configuration and direction of rotation are of the same sign for N,N-di-n-butyl-α-phenylethylamine, there was apparent retention of configuration to the extent of approximately 20% in the amine exchange reaction between d-(+)-N,N,N-trimethyl-α-phenylethylammonium bromide and di-n-butylamine. According to the previously stated rules for nucleophilic substitution, an S_N2 mechanism could definitely be ruled out. Retention is difficult to explain by means of an S_N1 mechanism for this particular compound since there should be no hindrance to the attainment of a planar structure and the phenyl group should serve to stabilize a carbonium ion (42). The possibility that the product could be slightly contaminated with an impurity having a very high dextro-rotatory value must be considered, although the infrared spectrum (Table IV) of this compound indicates only the

slightest impurity. If, instead of the α-phenylethyl group, one of the methyl groups migrated, N,N-dimethyl-α-phenylethylamine would be one of the products and, of course, would retain its configuration. A little less than 5% of this compound as an impurity would probably be capable of producing the rotation found experimentally. It is obvious from the low yield of product that other reactions were taking place, and the recovery of as much as 94% of the bromide from the original starting material as the hydrobromide of di-n-butylamine indicates that the quaternary ammonium salt reacted completely. It should be noted, however, that in a reaction course which would produce N,N-dimethyl-α-phenylethylamine no trimethylamine would be formed. As shown in Table V, the yield of trimethylamine in all the trials was considerably greater than that of the N,N-di-n-butyl-α-phenylethylamine. This lends support to the opinion that the yields of the latter were so low because of mechanical losses; however, the fact that trimethylamine could also be produced if styrene were one of the reaction products should not be ignored.

From the results obtained in this reaction, no general conclusions can be drawn regarding the mechanism of amine exchange reactions. The data obtained certainly indicate that the reaction is more probably of the S_N1 type than of the S_N2 type. In order to prove without a doubt that the reaction follows the S_N1 pattern, the kinetics of the

reaction should be studied, and proof should be obtained that the racemization occurs in the reaction itself and is not a result of the prolonged high temperatures in the reaction.

An apparent discrepancy in physical constants recorded in the literature presented another problem which might prove of interest for further investigation. Although no specific reference to N,N-dibutyl-α-phenylethylamine was found, a search of the literature revealed a reference to N,N-di-n-butyl-β-phenylethylamine with a recorded boiling point of 150-152° at a pressure of 13 mm. of mercury (43). A patent for the preparation of an unspecified isomer of N,N-dibutylphenylethylamine with a boiling point of 150° at a pressure of 2 mm. of mercury was also found (44). Its other constants also differed markedly from those of the N,N-di-n-butyl-α-phenylethylamine prepared in the course of this project. If it can be safely assumed that in the absence of a statement to the contrary the dibutyl amine used in the preparation of the compound claimed in the patent contained n-butyl groups, the conclusion must be that this compound is a substituted β-phenylethylamine, since the fact that our compound could be resolved into optical isomers is proof of the presence of the amino group on the alpha carbon. If there was no error in the recording of the boiling point of the compound covered by the patent or of the compound called N,N-di-n-butyl-β-phenylethylamine, they must be different compounds. The latter

might possibly be the same as the compound prepared in this laboratory, since the known N, N-di-n-butyl-α-phenylethylamine with its boiling point of 113-115° at a pressure of 2.8 mm. of mercury could very reasonably boil at 150° at a pressure of 13 mm. of mercury. Both the compounds recorded in the literature were prepared by the addition of dibutyl amine to styrene in the presence of sodium; however, different conditions of temperature and pressure were employed. Although the discrepancy is probably due to an error in recording, it is of interest.

SUMMARY

Stereochemical methods were employed in an attempt to shed light on the mechanism of amine exchange reactions between quaternary ammonium salts and primary and secondary amines.

The specific reaction studied was that between d-(+)-N, N, N-trimethyl- α-phenylethylammonium bromide and di-n-butylamine. Since physical constants for N, N, N-trimethyl- α-phenylethylammonium bromide were not found in the literature, the dl- and d-(+)- salts were prepared by means of the reaction of methyl bromide with the corresponding N, N-dimethyl- α-phenylethylamine. They were identified by the bromide content, which was determined by the Volhard method.

One of the products formed in the reaction studied was N, N-di-n-butyl- α-phenylethylamine. This previously unreported compound was prepared by two methods and was characterized for use in identification of the product of the reaction studied. In addition, the dextro-rotatory form was obtained from the resolution of the inactive amine by the use of d-tartaric acid and its specific rotation was determined. Preparation of l-(-)-N, N-di-n-butyl- α-phenylethylamine from l-(-)- α-phenylethylamine by a method which should not have disturbed

the carbon-nitrogen bond, served as a means of correlating configuration with direction of rotation. The N, N-di-n-butyl- α-phenylethylamine obtained from the reaction of d-(+)-N, N, N-trimethyl- α-phenylethylammonium bromide with di-n-butylamine showed approximately 20% retention of configuration.

In addition, α-phenylethylbromide and both optically active and inactive forms of N, N-dimethyl- α-phenylethylamine, which had been reported previously, were prepared by methods which varied slightly from those recorded in the literature.

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BIOGRAPHICAL NOTE

Betty Sue Gray was born on March 18, 1926, in Lakeland, Florida. After graduating from Lake Wales High School, she attended Florida State University where she received the B. S. degree cum laude in June, 1948. She entered graduate school at the University of Florida in September, 1948, and received an M. S. degree in 1951. During this time she held a graduate assistantship in the Department of Chemistry. After receiving this degree, she served as librarian at the Citrus Experiment Station of the University of Florida Agricultural Experiment Stations in Lake Alfred, Florida, until February, 1952. She then transferred to the Pulp and Paper Research Laboratory of the Engineering and Industrial Experiment Station of the University of Florida, where she held the position of Assistant in Research until September, 1954. Since that time she has held a Teaching Assistantship in the Department of Chemistry.

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This dissertation was prepared under the direction of the chairman of the candidate's supervisory committee and has been approved by all members of the committee. It was submitted to the Dean of the College of Arts and Sciences and to the Graduate Council and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

June 4, 1956

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